suppress AD gene-induced cell death observed in neurons is suggested to be the most important key for developing methods to treat AD.

VW 8/23/07

Please replace the paragraph beginning on page ~~1~~ 3, line ~~27~~ 1, with the following amended paragraph:

More specifically, a cDNA library was constructed from the brain of Alzheimer's disease (AD) patient, and was transfected into the F11/EcR/V642I cells mentioned above. Then a death trap screening operation was repeatedly performed to select cells that survived neuronal death induced by V642I APP. As a result, the present inventor succeeded in identifying a novel gene that protect cells against neuronal death induced by V642I APP. It was revealed that the clone, dubbed Humanin (HN) cDNA, encoding a novel polypeptide of 24-amino acids, suppresses neuronal death associated with AD. That is, the clone suppressed neuronal death induced by all of the known types of early-onset familial AD genes [V642I APP, K595N/M596L APP, M146L presenilin (PS)-1, and N141I PS-2] and by Aβ1-43. In contrast, the clone had no effect on neurotoxicity of polyglutamine repeat Q79, associated with Huntington's disease (HD)/spinocerebellar ataxia (SCA); and mutants of Cu/Zn-dependent superoxide dismutase (SOD1), associated with amyotrophic lateral sclerosis (ALS). HN mRNA was mainly produced in several organs other than the central nervous system. Transfection of HN cDNA into neurons led to transcription and production of expected peptides, which peptides were secreted into the culture medium up to a level of about 10 μM. The culture supernatant was enough active to demonstrate significant protection of cells from neuronal death induced by V642I APP. Synthetic HN polypeptide also showed neuroprotective action with similar dose-response properties against the four types of AD genes, and its suppression was maximal at 1 to 10 μM. Polypeptides expressed within neurons from a cDNA encoding an HN derivative, lacking secretion ability, failed to protect neurons from cell death. However, the same polypeptide synthesized and added to the culture medium showed protective action, which results indicate that the HN polypeptide acts from outside of the cell. Cys at position 8 and Ser at position 14 were found to be important according to an experiment detecting the activity of polypeptides

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Preferably, the sequence of Xn_1 includes, for example, sequences consisting of (Arg/Ala)-(Gly/Ala)-(Phe/Ala)-(Ser/Ala) (SEQ ID NO:96), and sequences with conservative substitution thereof. Herein, for example, "Arg/Ala" indicates Arg or Ala ("/" indicates that it is either one of the residues; the same is indicated throughout the description herein). Examples of such sequences include Arg-Gly-Phe-Ser (SEQ ID NO:63), Ala-Gly-Phe-Ser (SEQ ID NO:64), Arg-Ala-Phe-Ser (SEQ ID NO:65), Arg-Gly-Ala-Ser (SEQ ID NO:66), Arg-Gly-Phe-Ala (SEQ ID NO:67), and so on. Other examples include Arg-Gly-Ala-Ala (SEQ ID NO:68), Arg-Ala-Phe-Ala (SEQ ID NO:69), Arg-Ala-Ala-Ser (SEQ ID NO:70), Arg-Ala-Ala-Ala (SEQ ID NO:71), Ala-Gly-Phe-Ala (SEQ ID NO:72), Ala-Gly-Ala-Ser (SEQ ID NO:73), Ala-Gly-Ala-Ala (SEQ ID NO:74), Ala-Ala-Phe-Ser (SEQ ID NO:75), Ala-Ala-Phe-Ala (SEQ ID NO:76), Ala-Ala-Ala-Ser (SEQ ID NO:77), Ala-Ala-Ala-Ala (SEQ ID NO:78), and such. Conservative substitution can be exemplified by substitution within a group of amino acids, corresponding to conservative substitution, which will be described later. On the other hand, the sequence of Xn_2 preferably includes, for example, sequences consisting of (Leu/Ala)-(Leu/Ala), and sequences with conservative substitution thereof. Such sequences include Leu-Leu, Ala-Leu, Leu-Ala, and such. Ala-Ala can be also exemplified as such sequences. Furthermore, the sequence of Xn_3 preferably includes, for example, sequences consisting of (Glu/Ala)-(Ile/Ala)-(Asp/Ala)-(Leu/Ala) (SEQ ID NO:79), and sequences with conservative substitution thereof. Such examples include Glu-Ile-Asp-Leu (SEQ ID NO:80), Ala-Ile-Asp-Leu (SEQ ID NO:81), Glu-Ala-Asp-Leu (SEQ ID NO:82), Glu-Ile-Ala-Leu (SEQ ID NO:83), Glu-Ile-Asp-Ala (SEQ ID NO:84), and so on. Other examples are Glu-Ile-Ala-Ala (SEQ ID NO:85), Glu-Ala-Asp-Ala (SEQ ID NO:86), Glu-Ala-Ala-Leu (SEQ ID NO:87), Glu-Ala-Ala-Ala (SEQ ID NO:88), Ala-Ile-Asp-Ala (SEQ ID NO:89), Ala-Ile-Ala-Leu (SEQ ID NO:90), Ala-Ile-Ala-Ala (SEQ ID NO:91), Ala-Ala-Asp-Leu (SEQ ID NO:92), Ala-Ala-Asp-Ala (SEQ ID NO:93), Ala-Ala-Ala-Leu (SEQ ID NO:94), Ala-Ala-Ala-Ala (SEQ ID NO:95), and so on. The sequences of Xn_1, Xn_2, and Xn_3 may be selected from arbitrary combinations.

VW 8/23/07

Please replace the paragraph beginning on page ~~16~~ 23, line ~~8~~ 10, with the following amended paragraph: